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SCIENTIFIC ASPECTS AND WORKING DEFINITIONS FOR THE MANDATORY SCOPE OF THE CENTRALISED PROCEDURE

[REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 31 MARCH 2004]

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1. INTRODUCTION

With a view to harmonising the internal market for new medicinal products, article 3 and the Annex of Regulation (EC) No 726/2004 [1] (hereafter referred to as the "Regulation"), established that the centralised procedure should be made mandatory, in addition to new medicinal products manufactured by mean of biotechnology processes, also for orphan medicinal products and any medicinal product for human use containing a new active substance, *i.e.*, one that has not yet been authorised in the Community, for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder or diabetes, with effect from 20 November 2005.

Furthermore, with effect from 20 May 2008, the centralised procedure is also made mandatory for medicinal products for human use containing a new active substance for which the therapeutic indication is for the treatment of autoimmune diseases and other immune dysfunctions and viral diseases (recital 8 and Point 3 of the Annex to Regulation (EC) No 726/2004).

Accordingly, article 3 of Regulation (EC) No 726/2004 states that "no medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation".

The primary purpose of this discussion paper is to identify key scientific aspects and propose working definitions of the diseases appearing in the Annex to Regulation (EC) No 726/2004 (as opposed to other diseases), to clarify which therapeutic indication fall in the mandatory area of the centralised procedure for Marketing Authorisation Applications evaluation.

This document illustrates general principles, criteria used to clarify the definitions, and gives useful scientific details to facilitate the process of deciding whether a given proposed therapeutic indications for a new medicine falls in the mandatory areas as a treatment of the diseases described in point 3 of the Annex of the Regulation.

2. GENERAL PRINCIPLES

The general principles hereafter discussed are relevant only to medicinal products for human use containing entirely new active substances for treatment of diseases falling in the therapeutic areas mentioned above.

For the purposes of this paper "treatment" of a disease includes interventions that are specifically targeted at modifying the natural course of a disease, as defined following the proposed classification system set out hereafter. Typically, this includes causal or curative treatment of the disease. Thus, for example, the treatment of asymptomatic stages of diseases (e.g. early HIV-infection and in diabetes) is included into the mandatory scope of centralised procedure.

Medicinal products intended for symptom relief; diagnosing, staging, monitoring of the diseases; treatments of complications (e.g. diabetic neuropathy, diabetic retinopathy); treatment of adverse reactions caused by other treatments and medicinal products intended for primary prevention of the diseases, unless based on either disease-specific mechanisms (e.g. levodopa treatment in Parkinson's disease) or on treatment of the underlying disease (e.g. treatment of oesophageal obstruction caused by a malignant tumour) do not fall within the mandatory scope of the centralised procedure.

They may however fall under the mandatory scope of the centralised procedure according to other indents of the Annex to Regulation (EC) No 726/2004 EC[2].

[1] OJ L 136, 30.4.2004, p. 1.

[2] Applicants, may consider to use centralised procedure (through the optional scope) when medicinal products initially intended for preventive of diagnostic purposes have a development plan including the treatment of the diseases mentioned in the Annex.

Disease classification

The International Classification of Diseases version 10 (ICD-10) is proposed as the basis for disease classification[3] to aid in the recognition of disease conditions that are within the mandatory scope of the centralised procedure. In case of oncology, the International Classification for Diseases for Oncology (ICD-O) third edition is used[4]. Future updates of these classifications will be examined, as available, and implemented, if appropriate. However, the ICD classification may not include directly within one single section all conditions that may be classified as a relevant for the mandatory areas of treatment according to the above-mentioned principles. For those cases additional scientific considerations and guidance is provided in the areas-specific sections of this document.

Special cases

Where an application for marketing authorisation is planned and where the applicant or the competent authorities consider that there are doubts as to whether a therapeutic indication falls within the definition of treatment of a disease appearing in point 3 of the Annex to the (EC) No 726/2004, the applicant or the competent authorities are encouraged to seek the view of the EMEA to confirm whether the indication falls within the mandatory scope of the centralised procedure.

Products intended for a therapeutic indication falling within the scope of point 3 of the Annex to Regulation (EC) No 726/2004 which have started a mutual recognition or decentralised procedure before 20 May 2008 and have not yet been authorized in the Reference Member State, will be transferred to centralised procedure on 20 May 2008.

3. THERAPEUTIC AREAS WHERE CENTRALISED PROCEDURE IS MANDATORY FOR MARKETING AUTHORISATION APPLICATIONS

3.1 Acquired immuno-deficiency syndrome (AIDS)

"AIDS" defines a progressive and severe dysfunction of the immune system caused by the impairment of the immune response secondary to the Human Immunodeficiency Virus (HIV) infection. The HIV infection thus leads to a spectrum of clinical conditions ranging from a clinically unapparent infection, to the advanced disease. Therefore, and in line with the principles expressed above on viral diseases in general, causative treatment of the clinical condition should include also medicinal products intended to act on the HIV replication as such, even in absence of clinical symptoms, which occur at a later stage after the viral replication.

For the purpose of paragraph 3 of the Annex to Regulation (EC) No 726/2004 all products intended for the treatment of HIV-infection (symptomatic or not) will be within the scope of the centralised procedure.

Treatment of HIV/AIDS includes:

- Antiretroviral treatment, aimed at specifically blocking any step of the replication cycle of the HIV virus (e.g. reverse transcriptase, protease inhibitors, fusion inhibitors, integrase, etc)
- Immune therapies aiming at the elimination of the HIV or at the correction of the specific immune deficiency associated with HIV-infections

Note: medicinal products intended for the following interventions are not included in the mandatory scope of the centralized procedure (unless they belong to other categories within the mandatory scope of the Annex to Regulation (EC) No 726/2004):

- Diagnostics

[3] International statistical classification of diseases and related health problems - Tenth revision 1996. World Health Organization, Geneva, 1243 pp.
[4] International classification for diseases for oncology, third edition 2000. World Health Organization, Geneva, 240 pp.

- Prevention of HIV-infection unless the product belongs to other categories within the mandatory scope of the Annex to Regulation (EC) No 726/2004
- Treatment of HIV specific associated clinical conditions (e.g. infectious diseases)

3.2 Cancer

For the purpose of point 3 of the Annex to Regulation (EC) No 726/2004, cancer includes all malignant and borderline malignant neoplasms, following the current International Classification of Diseases for Oncology (ICD-O).

This includes primary or secondary malignant neoplasms, carcinoma in situ, and neoplasms classified as uncertain whether benign or malignant (behaviour codes /1, /2, /3, /6, /9).

Benign neoplasms (behaviour code /0) are not considered as cancer.

Medicinal products for cancer treatment include antineoplastic agents (including modulators and enhancers of antineoplastic activity) and adjuvant treatments (see Annex I).

Note: medicinal products intended for the following interventions are not included in the mandatory scope of the centralised procedure (unless they belong to other categories within the mandatory scope of the Annex to Regulation (EC) No 726/2004):

- Agents developed to prevent or treat side-effects of cancer treatment (e.g., neutropenia, nausea and vomiting, tumour lysis syndrome).
- Diagnostic agents aimed at diagnosing, staging or monitoring of the disease
- Agents intended to reduce the risk or prevent cancer or to treat pre-cancerous lesions
- Agents intended to treat cancer associated symptoms (e.g. cancer pain)

3.3 Neurodegenerative diseases

Neurodegenerative diseases are a group of chronic progressive conditions with diverse/unknown aetiologies. Thus, it is not possible to define this group of diseases on the basis of common aetiological or pathogenesis mechanisms.

Thus, for the purpose of paragraph 3 of the Annex to Regulation (EC) No 726/2004, neurodegenerative diseases are defined on the basis of international agreement, ICD-10 classification.

The scope includes ICD-10 codes G10 to G13, G20, G23 to G25, G30, and G31 (few exceptions, see Annex II).

It also includes neurodegenerative diseases of the sense organs such as hereditary optic neuropathy, pigmentary degeneration of the retina, etc.

Treatment of neurodegenerative diseases includes:

- Symptomatic treatment, when symptoms are directly caused by neurodegeneration and when the treatment is based on either disease-specific mechanisms (e.g. levodopa treatment in Parkinson's disease) or on treatment of the underlying disease.
- Neuroprotective treatment (slowing/arrest of symptom progression)
- Curative treatment in terms of restoration of neuronal function

Note: medicinal products intended for the following interventions are not included in the mandatory scope of the centralised procedure (unless they belong to other categories within the mandatory scope of the Annex to Regulation (EC) No 726/2004):

- Primary prevention of these diseases
- Diagnostics of these diseases
- Treatment of symptoms that are not directly related to neuro-degeneration

3.4 Diabetes

For the purpose of paragraph 3 of the Annex to (EC) No 726/2004 the term diabetes means *diabetes mellitus.* According to the International Classification of Diseases five main types of *diabetes mellitus* are currently identified on the basis of their aetiology (ICD-10 codes E10 to E14; see Annex III of this document).

The term diabetes mellitus defines progressive metabolic dysfunctions triggered by the impairment of glucose metabolism - either primary or secondary to a large range of causal factors - and leading to a spectrum of clinical conditions ranging from an asymptomatic stage to the advanced disease, with various organ-system complications.

Treatment of *diabetes mellitus* includes

- agents controlling the glycaemia levels and glycosylated haemoglobin levels.
- therapies aiming to stop an ongoing loss of insulin-producing cells

Note: medicinal products intended for the following interventions are not included in the mandatory scope of the centralised procedure (unless they belong to other categories within the mandatory scope of the Annex to Regulation (EC) No 726/2004):

- Agents aimed at treating or preventing diabetic specific complications (such as the diabetic retinopathy, the diabetic nephropathies and the diabetic peripheral neuropathy)
- Primary prevention
- Diagnostics

For the purposes of this paper the disease Diabetes insipidus is not included in the definition of "diabetes".

3.5 Viral diseases

The viral diseases present with a spectrum of clinical signs ranging from those in an asymptomatic stage to advanced disease, with variable clinical characteristics such as acute onset and benign or serious outcomes, as well as with indolent and subtle onset and then with chronic and sometimes devastating consequences.

Treatment of the viral infections should include all medicinal products intended to act on the viral entry to host cells, replication and subsequent spreading to other cells, even in absence of clinical symptoms, which may occur at a later stage after the viral replication started (e.g. chronic viral hepatitis).

For the purpose of paragraph 3 of the Annex to Regulation (EC) No 726/2004 all products intended for the treatment of viral infections (symptomatic or not) will be within the scope of the centralised procedure.

The ICD 10 appears to be an useful classification including most of the viral infections in a large general B class complemented by groups of viral diseases listed under organ specific classes (group A) taking in to account the organ-elective tropism of the viruses, e.g.:
–Viral diseases characterized by skin and mucous membranes lesions
–Viral hepatitis
–HIV (addressed in the subsequent section of this document)
–Other viral diseases (epidemic myalgia, viral carditis)

The classification moreover provides for viral diseases organised by target organ(s), or by mode of transmission, e.g.

•A 08 Viral and other specified intestinal infections (rotaviral, adenoviral etc.)
•A 60 Infections with a predominant sexual mode of transmission (herpes genitalis, HIV)
•A 80 Viral infections of the CNS (polio.rabies meningitis) and atypical viral diseases (CJD, prion disease etc.)

•A 90 Arthropode-borne viral fevers (dengue, yellow fever, haemorrhagic fever)

Products intended for the following aspects are not included in the scope of treatment of viral infections (unless they belong to other categories within the mandatory scope of the Annex to Regulation (EC) No 726/2004):

- Diagnostics
- Preventive vaccines
- Treatment of associated clinical conditions and complications (e.g. bacterial infectious diseases)

CHMP scientific opinion might have to be considered in special circumstances, e.g. when new scientific knowledge is emerging of a role of viruses in a given disorder.

3.6 Autoimmune diseases and other immune dysfunctions

Under this term a large spectrum of medical conditions may be included, which are classified in a very variable manner, depending on whether the focus of the classification is on the clinical phenotype or on the specific immune dysfunction involved in the pathogenesis of the conditions.

There is a number of common traits associated to immune-system based diseases characterized by abnormal activation of immune system pathways such as: genetic background, hormonal status, triggering extrinsic factors (e.g. infections), a latent phase often preceding the clinical symptoms and signs, potential progressive multi-organ involvement, initial response to steroids or immune suppressants.

The understanding of the role of the immune system in various diseases is still incomplete. Therefore, it is not possible to give a final exhaustive list of diseases that will fall into this category.

Nevertheless, the common denominator for these diseases is the presence of abnormal immunological findings, such as lack of immunological tolerance to auto-antigens, an inappropriate immune response against normal environmental or dietary antigens as well as a failure to initiate or down-regulate a normal immune reaction.

The autoimmune diseases and other immune dysfunctions on scientific grounds can be classified as follows:

1. auto-immune diseases: systemic or organ-specific

2. primary immuno-deficiency syndromes involving
   - T-cells
   - B-cells
   - Complement
   - Other elements necessary for a proper immune response

3. Inappropriate immune response such as hypersensitivity

4. Lymphoproliferation due to defective regulation of the immune system

5. Immune-complexes diseases

Auto-immune diseases and in particular ‘other immune dysfunctions’ based on the classification mentioned above encompasses a very wide range of diseases including rheumatoid arthritis (and all ‘disease-modifying’ drugs for that use) and a range of dermatological diseases such as psoriasis . As the role of the immune system in some diseases is still not completely understood, it is suggested that the preliminary list be limited initially to systemic (rather than single organ) diseases known to result

directly and mostly from intolerance to auto-antigens or from unregulated immune reactions such as those in the main ICD 10 classification.

A tentative list of conditions which may be included under the above classification (not exhaustive, based on ICD 10 with some complementary information derived for established reference in the field) is given in Annex IV. To assist sponsors and regulatory authorities, the preliminary list indicates conditions included in the mandatory areas of centralized procedure and will be updated periodically.
It needs to be updated over time based on state-of-the-art scientific evidence for autoimmunity or immune dysfunctions being directly associated with a clinical condition.

Note: Medicinal products active in such conditions but not directly intervening in the immuno-pathology of the disease (e.g. Beta agonists for the treatment of asthma) will not be considered as falling within the mandatory scope of the centralised procedure, unless they belong to other categories within the mandatory scope of the Annex to Regulation (EC) No 726/2004.

In case of doubt the sponsors and the experts within the NCAs are encouraged to seek the opinion of the CHMP to confirm whether the indication of such products falls within the mandatory scope of the centralised procedure.

ANNEX I (Cancer)

Antineoplastic treatment includes chemotherapy, biologic therapies and hormonal agents that produce antitumour cytotoxic or cytostatic effects, or therapies that increase sensitivity of malignant cells to other antineoplastic treatments (including radiosensitizers).

Traditionally, chemotherapy has a role in four different clinical settings:

1) Induction treatment for advanced disease (induction chemotherapy): therapy given as the primary treatment for patients who present with advanced cancer for which no alternative treatment exists.

2) As an adjunct to local treatment (adjuvant chemotherapy): use of systemic treatment after the primary tumour has been controlled by an alternative modality, such as surgery and radiation therapy.

3) Primary treatment (primary chemotherapy, or neoadjuvant chemotherapy): chemotherapy as the initial treatment for patients who present localized cancer for which there is an alternative but less than completely effective local treatment

4) local treatment by direct instillation into sanctuary sites or by site-directed perfusion of specific regions directly affected by the cancer

Medicinal products given without curative intent but with the aim of achieving pain or other symptom palliation (palliative care) **via anti-tumour effects** are considered anti-neoplastic treatment. Hormonal agents used in hormonally responsive cancers such as breast, prostate or endometrial carcinomas are considered antineoplastic treatment.

However, for the purpose of point 3 of the Annex to Regulation (EC) No 726/2004, the following are not considered products for cancer treatment: hormonal agents used to treat symptoms caused by cancer without anti-tumour effect as well as other agents intended to treat cancer associated symptoms e.g. supportive and palliative care treatments (without curative intent of the cancer), such as analgesic drug therapy (opioids, non-opioid drugs), local anaesthetics, corticosteroids for the management of pain, bone resorption inhibitors used as adjuvants for bone pain, antidepressants, anticonvulsants.

ANNEX II (Neurodegenerative diseases)

(Please note that the following listing is an extract from the International statistical classification of diseases and related health problems - Tenth revision 1996. World Health Organization, Geneva, 1243 pp.)

ICD-10 codes for Neurodegenerative diseases

G10 Huntington's disease

G11 Hereditary Ataxia

G12 Spinal muscular atrophy and related syndromes

G13 Systemic atrophies primarily affecting central nervous system in diseases classified elsewhere

G20 Parkinson's disease

G23 Other degenerative diseases of the basal ganglia

G24 Dystonia (except for drug-induced dystonia)

G25 Other extrapyramidal and movement disorders: G25.0 Essential tremor

G25.2 Other specified forms of tremor (intention tremor)

G30 Alzheimer's disease

G31 Other specified degenerative diseases of nervous system not elsewhere classified (except for degeneration of nervous system due to alcohol)

ANNEX III (Diabetes)

(Please note that the following listing is an extract from the International statistical classification of diseases and related problems – Tenth revision 1996. World Health Organization, Geneva, 1243 pp.)

ICD-10 codes for Diabetes mellitus

E10: Insulin-dependent diabetes mellitus

Includes: diabetes (mellitus):

- brittle
- juvenile-onset
- ketosis-prone
- type I

E11: Non-insulin-dependent diabetes mellitus

Includes: diabetes (mellitus) (non-obese/obese):

- adult-onset
- maturity-onset
- nonketotic
- stable
- type II
- non-insulin-dependent diabetes of the young

E12: Malnutrition-related diabetes mellitus

E13: Other specified diabetes mellitus

E14: Unspecified diabetes mellitus

ANNEX IV (Autoimmune diseases and other immune dysfunctions)

(Please note that the following listing is an extract from the International statistical classification of diseases and related problems – Tenth revision 1996. World Health Organization, Geneva, 1243 pp.)

ICD M30 Systemic (including connective tissue within the musculoskeletal system) autoimmune disorders

Includes:

- Systemic Lupus Erythematosus (SLE)
- Systemic sclerosis
- Dermatopolymyositis
- Polyarteritis nodosa
- Spondyloarthropathies
- Sjogren's syndrome
- Rheumatoid arthritis (RA) including Juvenile RA
- Ankylosing spondylitys

ICD D50 Diseases of the blood and blood forming organs

Includes:

- Autoimmune thrombocytopenia
- Idiopathic Thrombocytopenic Purpura and other

ICD D70 Other diseases of blood forming organs

Includes:

- Histiocytosis
- Functional disorders of Polymorphonuclear cells (PMN)

ICD D80 Certain disorders involving the immune mechanisms

Includes:

- Combined immunodeficiency
- Sarcoidosis
- Primary immunodeficiency diseases

Other immune dysfunctions and autoimmune diseases relevant to organ systems are scattered throughout the various organ classes of the ICD 10 classification, and include:

- Idiopathic uveitis
- Autoimmune liver diseases –primary biliary cirrhosis
- Thyroiditis (Grave's, Hashimoto)
- Multiple sclerosis
- Addison' s disease
- Myasthenia gravis
- Pemphigus, Psoriasis
- Chronic GVHD
- Haemolytic disease of the newborn (rhesus immunisation, e.g. anti-D)
- Vasculitis Syndromes with underlying immunopathogenic mechanism: Wegener, Panarteriitis nodosa